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Thromboxane Inhibition Improves Renal Perfusion and Excretory Function in Severe Congestive Heart Failure

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OBJECTIVES The aim of this study was to evaluate whether thromboxane inhibition can favorably affect renal perfusion and clinical conditions in patients affected by severe heart failure.

BACKGROUND The renal formation of the vasoconstrictor thromboxane A_2 (TxA_2) is increased during cardiac failure.

METHODS By oral administration of picotamide (a renal TxA_2 synthase and TxA_2/prostaglandin H_2 receptor inhibitor), we blocked renal TxA_2. Fourteen patients in New York Heart Association functional class IV were studied according to a randomized, double-blinded, cross-over design. Each of the two eight-day periods of testing was preceded by a three-day period during which certain vasoactive medications were stopped.

RESULTS Daily 24-h total urinary thromboxane B_2 (TxB_2), the stable metabolite of TxA_2, dropped at the end of picotamide treatment ($p < 0.01$ vs. baseline). Compared with placebo, effective renal plasma flow and the glomerular filtration rate increased ($p < 0.01$ and $p < 0.05$, respectively), thus leading to a significant decrease in the filtration fraction ($p < 0.01$). Renal vascular resistance decreased consistently ($p < 0.01$). In all patients, picotamide treatment was associated with an increase in diuresis and natriuresis ($p < 0.001$ vs. baseline). Plasma creatinine decreased ($p < 0.05$ vs. baseline). Patients also showed improvement in several clinical parameters, including a significant decrease in both pulmonary and venous pressure ($p < 0.01$ vs. baseline).

CONCLUSIONS These results indicate that renal thromboxane formation plays an important role in renal vascular resistance in patients with severe heart failure, such as those described in the present study. Inhibition of TxA_2 improves renal hemodynamics and kidney function and favorably affects indexes of cardiac performance. (J Am Coll Cardiol 2003;42:133–9) © 2003 by the American College of Cardiology Foundation

Chronic congestive heart failure (CHF) is characterized by the activation of neurohormonal vasoconstrictive pathways. These include the sympathetic nervous system, the renin-angiotensin system, vasopressin, and endothelin (1–4). The neurohormonal effects contribute to maintaining effective plasma volume by stimulating the tubulo-glomerular feedback mechanism (2). This mechanism is associated with a progressive decline in renal plasma flow and an increase in the filtration fraction (FF) due to selective constriction of the efferent arterioles (5–7) to preserve glomerular filtration. The increased formation of vasoconstrictor mediators is associated with enhanced formation of systemic and renal vasodilative factors, such as cardiac natriuretic peptides and renal prostaglandin (PG)E_2 and PGI_2 (1,8). Renal PGE_2 and PGI_2 counteract vasoconstriction, hence contributing to the maintenance of intrarenal circulatory homeostasis (9). A progressive increase in renal production of vasoconstrictor eicosanoids, such as $PGF_{2\alpha}$ and thromboxane A_2 (TxA_2), occurs in the more advanced stages of CHF (10). This increase most likely results in a decrease in renal blood flow, as suggested by experimental studies (11–13). Thromboxane A_2 promotes tubulo-glomerular feedback in microperfused single-nephron preparations (14). It causes renal vasoconstriction when injected in animals (11), thus resulting in increased sodium and water retention.

Under physiologic conditions, TxA_2 renal production in humans is low and does not play any role in renal hemodynamics (15). In pathophysiologic conditions such as CHF, renal function can remarkably worsen in the presence of large and persistent increases in renal TxA_2 formation (10). To investigate renal TxA_2 formation and its role in renal hemodynamics in patients with severe CHF, we used a TxA_2 synthase and TxA_2/PGH_2 receptor inhibitor called picotamide (16). Several clinical trials have shown that picotamide can effectively block TxA_2 activity, thus resulting in good clinical effects (17–19).

METHODS

Patient selection. We investigated 14 patients in New York Heart Association (NYHA) functional class IV (10 males and 4 females; mean age 70 ± 10 years). The

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CHF = congestive heart failure
ERPF = effective renal plasma flow
FF = filtration fraction
GFR = glomerular filtration rate
mPAP = mean pulmonary artery pressure
NYHA = New York Heart Association
PG = prostaglandin
RIA = radioimmunoassay
RVR = renal vascular resistance
TxA_2 = thromboxane A_2
TxB_2 = thromboxane B_2
UCr = urinary creatinine

demographic and clinical characteristics of the patients are reported in Table 1. Patients enrolled in the study had chronic CHF due to idiopathic dilated cardiomyopathy (n = 3), ischemic dilated cardiomyopathy (n = 10), and mitral regurgitation (n = 1). The patients with ischemic dilated cardiomyopathy had a previous (more than six months before the start of the study) myocardial infarction; none of them reported any episodes of angina during testing or for six months before the start of the study. No patients had clinically detectable edema or pulmonary rales. Patients who were enrolled in this study required hospitalization due to the inability for home treatment of NYHA functional class IV CHF. Because aspirin and nonsteroidal anti-inflammatory drugs can interfere with the effects of picotamide, patient selection criteria were also based on the exclusion of the use of aspirin or angiotensin-converting enzyme (ACE) inhibitors.

Patients with diabetes, liver or renal disease, malignancies, or serum creatinine levels ≥2.0 mg/dl were excluded from the study. The investigation followed the principles of the Declaration of Helsinki. All patients gave their informed, written consent to participate in the study after a clear and thorough explanation of the program had been presented.

Table 1. Patient Characteristics and Medications

Etiology	
Ischemic heart disease (%)	10 (71)
Dilated cardiomiopathy (%)	3 (21)
Valvular heart disease (%)	1 (8)
Baseline hemodynamic characteristics	
EF on echocardiography (%)	27 ± 10
Mean BP (mm Hg)	94.3 ± 11.4
HR (beats/min)	78.5 ± 7.3
Medications throughout the study	
Digoxin 0.125–0.25 mg once or twice daily	14
Furosemide 25–125 mg once or twice daily	14
Canrenoate potassium 100 mg orally twice daily	7
Medications discontinued before admission	
Captopril 25 mg twice daily	4
Ramipril 2.5–5 mg twice daily	4

Data are presented as the number (%) of patients.
BP = blood pressure; EF = ejection fraction; HR = heart rate.

Study design. The study was designed as a randomized, double-blinded, placebo-controlled, cross-over study. The patients were treated with digitalis, diuretics, and nitrates. Before hospitalization, two patients with atrial fibrillation had been on oral anticoagulants; during the study, they continued this treatment (international normalized ratio 2.5 to 3.0). Administration of digitalis, vasodilators, and diuretics was continued at the pre-established optimal dosage. Given that ACE inhibition can stimulate prostaglandin and thromboxane formation via bradykinin activation (20,21), ACE inhibitor administration was discontinued during the 48 h before the beginning the study and during the study. To prevent any possible deterioration in the clinical picture due to the withholding of ACE inhibitors, the enrolled patients were kept under strict, close, continuous clinical surveillance during the whole trial period. Only those patients whose conditions had remained stable after the first 12 h after ACE inhibitor discontinuation were admitted into the study. Patients remained under surveillance during the entire period of hospitalization until the end of the study. Initially, 20 patients had been selected, but only 14 were admitted into the study (6 patients had shown signs of instability during the 12-h pretreatment evaluation period). To obtain an index of the modifications of the patients' clinical status (during testing), we evaluated the variations in tachycardia, breathlessness, and the occurrence of pulmonary rales and clinically detectable edema (before, during, and after the testing period). Evaluation was carried out twice by two cardiologists, neither of whom had any knowledge of the laboratory results, tests carried out, and/or treatment. During the total hospital period, the subjects were kept on a daily diet that contained 100 mmol of sodium chloride and 60 to 80 mmol of potassium. Dietary compliance with sodium intake was checked by measuring urinary sodium. Daily fluid intake was checked so that a constant water balance was maintained during the three-day pretreatment period. Patients received two tablets per day of either placebo or picotamide (600 mg, orally). After eight days of treatment, the patients underwent a three-day washout period before crossing over to the other treatment arm for a second eight-day period. The urine sample from the first day of the two eight-day periods was used to determine baseline values. On the second, fourth, sixth, and eighth days of both treatment periods, serum and urinary electrolytes, 24-h urinary volume, and 24-h urinary thromboxane excretion were measured. On the eighth day of both treatment periods, we studied renal hemodynamics. This experimental design allowed for a comparison between the treatment and placebo effects on renal hemodynamic parameters, without the need to expose the patients to any additional radioisotopic clearance studies.

Systemic hemodynamic parameters. Blood pressure and heart rate were recorded on an average of six times a day (at 6:00, 8:00, and 12:00 AM and 4:00, 8:00, and 12:00 PM). Results were used as an index of the 24-h study period. They were also used to control levels of hypotension (a

symptomatic sudden and/or persistent decline in arterial systolic blood pressure <105 mm Hg) and/or orthostatic hypotension (i.e., a drop in systolic blood pressure ≥20 mm Hg or in diastolic blood pressure ≥10 mm Hg) (22). Mean pulmonary artery pressure (mPAP) was measured by Doppler echocardiography on day 0 before the start of each eight-day period and on days 2, 4, 6, and 8 of each testing period. In one patient not showing tricuspid insufficiency, the pulmonary acceleration time was used to estimate mPAP, given that the two have been shown to be directly and strongly correlated (23). If tricuspid regurgitation was present, the atrioventricular pressure gradient was used to estimate mPAP, as described elsewhere (24). Venous pressure was obtained directly (25) through an antecubital vein.

Renal excretory function. Blood urea nitrogen, serum creatinine, serum and urinary sodium, and water excretion were monitored every other day throughout the hospital period. Urinary and serum sodium and potassium were measured by using a flame photometer (Instrumentation Laboratory, Lexington, Massachusetts).

Renal hemodynamics. At the end of the two periods of the study, two radioisotopes were rapidly injected into an antecubital vein with a 20-gauge needle, (iodine-125 [iothalamate] and iodine-131 [hippurate], both at a dose of 1 μCi/kg in a total volume of 9 ml). Six-milliliter blood samples were withdrawn from the other antecubital vein at 2, 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 min after isotopic injection. Blood samples were immediately centrifuged and a 3-ml plasma volume was measured for 5 min with a gamma ray, well-counter spectrometer (Packard Instrument Company, Palo Alto, California). Effective renal plasma flow (ERPF) and the glomerular filtration rate (GFR) were measured according to the methods described by Sapirstein et al. (26). The obtained values were normalized to a standard body surface area of 1.73 m^2.

Urinary TxB_2 measurement. Immediately after collection, the urine was frozen and stored at −20°C until extraction and purification procedures could be carried out. Renal thromboxane B_2 (TxB_2) was measured by radioimmunoassay (RIA), as reported elsewhere (27). A tritium tracer RIA was performed after allowing four to five months for the radioactivity of the iodine-125 and -131 in the urine to decay to background levels so as not to interfere with the TxB_2 RIA (28). Furthermore, before processing the urine for RIA, each sample was placed in a gamma counter to rule out any residual radioactivity. The data are expressed as ng/g of 24-h urinary creatinine to normalize the detected values according to the changes in renal function.

Statistical analysis. Continuous variables are expressed as the mean value ± SD. Discrete variables are expressed as percentages. Comparisons between groups in basal conditions were performed by using the Student *t* test. Before analyzing the effects of the treatments on the different clinical parameters examined, we compared the baseline values with those obtained after the washout period, at the beginning of the second part of the study. We first tested for the presence of any differences within the same group, then between groups with the paired *t* test and Student *t* test, respectively. Given the lack of any dissimilarity (data not shown), we performed a general linear model for repeated measures to assess the effects of picotamide and placebo; patient data were pooled according to treatment. Comparisons between each observation time within each treatment group were performed in the same model specifying that the baseline value was reference one and testing for the presence of any statistically significant differences at days 2, 4, 6, and 8 ("simple" method) (29). Finally, we searched for differences between groups at each step of the study by using the Student *t* test. A value of $p < 0.05$ was considered statistically significant. Given that 20 patients were initially selected, but only 14 were admitted to the study after ACE inhibitor suspension, we performed a retrospective power analysis to evaluate whether the sample size was appropriate. Assuming a mean value of TxB_2 excretion of 900 ± 122 ng/24 h for the 14 subjects enrolled, we built a model with a two-tailed alpha level of 0.05, obtaining a precision in estimating a difference in the population of 67 ng/24 h. According to this estimate, for the difference of 468 ng/24 h in TxB_2 excretion observed in the study, the power was >99.9%.

RESULTS

Effects of placebo administration. No adverse clinical events or severe hypotension occurred during placebo administration. During placebo administration, no change was found in urinary TxB_2 excretion (926 ± 154 vs. 878 ± 126 ng/g urinary creatinine [UCr]/24 h [first vs. eighth day], p = NS) (Fig. 1). Because renal and hemodynamic parameters at baseline were similar both before treatment and in the placebo periods, the three-day washout period appeared sufficient to abolish the effects of picotamide. There were not significant changes during the eight days on placebo.

Effects of picotamide treatment. A significant decrease in urinary TxB_2 was observed during the period of active treatment ($p < 0.001$) (Fig. 1). By the sixth day, urinary TxB_2 significantly dropped with respect to baseline (557 ± 138 vs. 900 ± 122 ng/g UCr/24 h; −38.2%; $p < 0.01$) and reached its minimum on the eighth day of picotamide treatment (432 ± 117 vs. 900 ± 122 ng/g UCr/24 h; −52.1%; $p < 0.01$). Moreover, compared with placebo, a significant decrease in urinary TxB_2 was observed on the sixth day (557 ± 138 vs. 893 ± 148 ng/g UCr/24 h; −37.7%; $p < 0.01$) and on the eighth day of picotamide treatment (432 ± 117 vs. 878 ± 126 ng/g UCr/24 h; −50.8%; $p < 0.01$) (Fig. 1).

The modifications in thromboxane excretion were accompanied by significant changes in renal hemodynamics, as shown in Figure 2. When comparing active treatment with placebo treatment, picotamide administration increased ERPF (+31.4%, $p < 0.002$) more than GFR (+7.9%, $p < 0.05$ vs. placebo), thus leading to a reduction

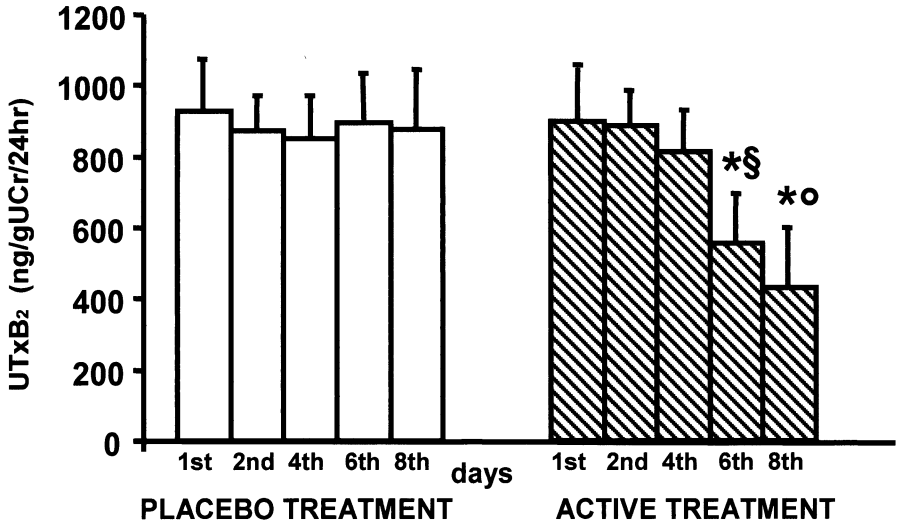

Figure 1. Urinary thromboxane B_2 ($UTxB_2$) levels (ng/g UCr/24 h) during the two treatments: placebo **(open bars)** and active treatment **(hatched bars)**. *$p < 0.01$ vs. day 6 of placebo; °$p < 0.01$ vs. day 8 of placebo; §$p < 0.01$ vs. baseline.

in FF (−16%, $p < 0.01$ vs. placebo). The overall renal vascular resistance (RVR) decreased substantially (−26.8%, $p < 0.01$ vs. placebo) (Fig. 2).

Table 2 reports the effect of active treatment on the different parameters assayed. We noted in all patients a decrease in both mPAP (−20.6% vs. baseline, $p < 0.001$) and venous pressure (−37.5%, $p < 0.01$); this effect was associated with clinical improvement, as indicated by a reduction in symptoms and increased sodium and water excretion. Blood pressure did not vary during treatment, whereas the heart rate significantly decreased. Picotamide treatment resulted in clinical improvement leading to dyspnea reduction and a decrease in tachycardia. Body weight significantly decreased on day 8 (−3.5%, $p < 0.01$ vs. day 1) of picotamide treatment. No bleeding, hypotension, or other adverse clinical events occurred during picotamide administration.

DISCUSSION

Thromboxane inhibition by picotamide and renal function. In severe CHF, picotamide administration inhibited renal thromboxane production in our patients who were not exposed to beta-adrenergic blockade or angiotensin activity suppression. The inhibition of renal thromboxane was consistent with the drop in urinary TxB_2, which is a metabolite of renal TxA_2 formation and not of platelet TxA_2 (30). Blockade of the renal effects of TxA_2 led to a partial recovery of renal hemodynamics, as indicated by the 31.4% increase in ERPF and 26.8% decline in RVR. The renal resistance represents a very important part of total peripheral vascular resistance, and its increase occurs soon during the onset of CHF, thus leading to augmentation of the cardiac work load. The increases in ERPF and GFR following renal TxA_2 inhibition most probably indicate that the exaggerated TxA_2 release in CHF participates in constriction of the renal resistance vessels and likely with selective activity on afferent arterioles. This interpretation is in agreement with a recent study providing evidence that the afferent glomerular arteriole is the vascular segment that is preferentially constricted by TxA_2 (12). Inhibition of TxA_2 can lead to renal vasodilation, even in the absence of ACE inhibitors, highlighting the importance of the overproduction of renal thromboxane in the pathophysiology of CHF. The effects of picotamide were investigated in a cross-over experimental design where all patients were under controlled daily sodium intake, and the therapy remained unmodified during the whole study. The only variable was picotamide versus placebo administration. The lack of variations in renal function during placebo and the hemodynamic changes observed after picotamide administration should most probably not be interpreted as regression to the mean but most likely as real modification and improvement.

The improvement in renal function appeared to be related to the drop in pulmonary artery pressure and venous pressure, both associated with inhibition of renal thromboxane activity. The functional effects of TxA_2 inhibition became evident on the eighth day of picotamide administration. This latency seems to be dependent on the cumulative activity peculiar to this drug (18).

TxA_2 and renal pathophysiology in heart failure. In CHF, sympathetic activation and enhanced activity of the renin-angiotensin system, as well as vasopressin, play a major role in maintaining perfusion pressure and blood volume (2). An increase in renal formation of vasodilating PGE_2 and PGI_2 occurs in the early stages of heart failure (8) and can modulate the effects of vasoconstrictor mediators (1,9). This increase in vasodilating eicosanoid formation helps to sustain adequate renal glomerular filtration (1). With the progressive reduction in renal blood flow in the

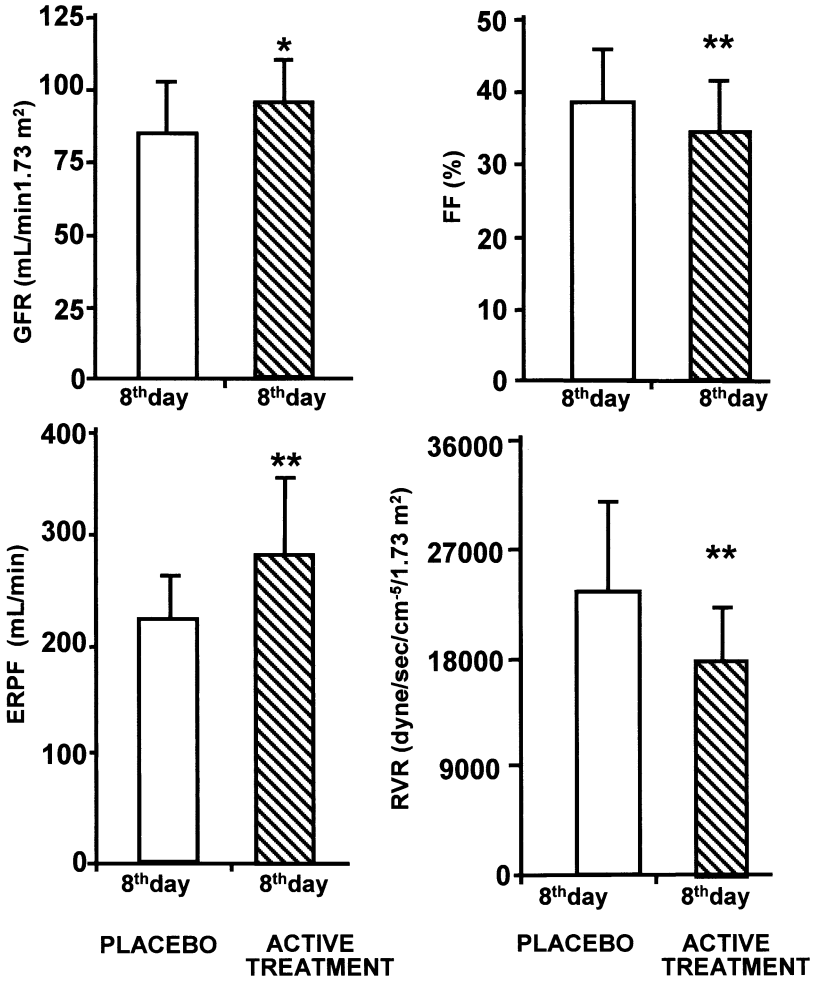

Figure 2. Effects of thromboxane A_2 inhibition on renal hemodynamics. **Open bars** = placebo; **hatched bars** = active treatment. *$p < 0.05$ vs. day 8 of placebo; **$p < 0.01$ vs. day 8 of placebo. ERPF = effective renal plasma flow; FF = filtration fraction; GFR = glomerular filtration rate; RVR = renal vascular resistance.

advanced phases of CHF (i.e., patients in NYHA functional class III and especially class IV), TxA_2 formation is enhanced (10), thus increasing the RVR. The increased TxA_2 formation results in the upset of the fine balance between renal vasoconstrictor and vasodilating systems. The inhibition of TxA_2 activity causes an increase in ERPF with decrease in RVR, resulting in enhanced water and sodium excretion. Furthermore, the inhibition of TxA_2 synthesis augments the availability of arachidonic acid, which is used for the synthesis of vasodilating PGs (31,32). In addition to its influence on renal hemodynamics, TxA_2 can potentiate tubulo-glomerular feedback by activating the sensory component in the macula densa (32).

In summary, the favorable effects of TxA_2 inhibition on renal function in patients with advanced CHF may be the consequence of three coexisting and interrelated mechanisms: 1) inhibition of the direct vasoconstrictive effect of renal TxA_2 on the afferent arterioles and mesangial cells; 2) enhancement of vasodilating PG synthesis due to the increased availability of arachidonic acid endoperoxides (PGG_2 and PGH_2) for renal formation of PGE_2 and PGI_2; and 3) reduction of the tubulo-glomerular feedback activation.

To our knowledge, no study has addressed the problem of picotamide action directly on the single nephron. Therefore, we cannot exclude the possibility that the natriuretic, kaliuretic, and diuretic effects of picotamide may have been partly due to some direct picotamide tubular action.

Study limitations. It is not possible to transfer the results obtained in our trials to all patients with heart failure, especially those who are usually treated with aspirin and/or ACE inhibitors. Such patients were excluded from the study, as were those patients with serious renal dysfunction (i.e., patients with creatinine >2 mg/dl). This latter complication can confound the evaluation of renal function after picotamide administration.

Conclusions. Our results suggest that increased renal TxA_2 formation is an important component of the complex pathophysiology of heart failure and that inhibition of renal thromboxane activity notably improves kidney function. However, no conclusions can be drawn regarding the use of

Table 2. Effect of Picotamide Administrations on Hemodynamic, Serum, and Urinary Variables

		Day			
	Baseline	2	4	6	8
HR (pulse/min)	79.2 ± 4.7	76.1 ± 5.1	76.4 ± 4.9	71.9 ± 2.7*	70.6 ± 5.4*†
SBP (mm Hg)	124.6 ± 17.0	118.2 ± 13.7	130.4 ± 14.4	125.0 ± 14	126.4 ± 18.5
DBP (mm Hg)	76.0 ± 6.3	76.8 ± 8.7	79.2 ± 7.6	74.3 ± 7.0	79.9 ± 6.7
mPAP (mm Hg)	50.4 ± 12.3	49.9 ± 13.2	47.9 ± 9.60	47.5 ± 10.9	40.0 ± 9.6†‡
VP (mm Hg)	6.6 ± 1.3	—	—	—	4.1 ± 1.1*§
SCr (mm/dl)	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.4	1.3 ± 0.4	1.1 ± 0.4†‡
UCr (g/24 h)	1.1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3‡¶	1.3 ± 0.4‡¶	1.4 ± 0.4‡‖
BUN (mg/dl)	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.5 ± 0.1‡§
SNa (mmol/dl)	139.1 ± 2.1	140.2 ± 3.4	139.7 ± 3.7	139.5 ± 3.5	139.6 ± 2.0
SK (mmol/dl)	3.9 ± 0.3	4.1 ± 0.3	4.1 ± 0.4	4.0 ± 0.4	4.0 ± 0.3
UV (ml/24 h)	1,300 ± 403	1,292 ± 226	1,392 ± 255	1,542 ± 277	1,664 ± 267‡§
UNa (mmol/24 h)	88.8 ± 21.2	92.4 ± 28.8	103.8 ± 31.8	111.0 ± 33.1	138.1 ± 34.6*‖
UK (mmol/24 h)	42.4 ± 10.5	47.9 ± 12.6	46.0 ± 9.6	47.4 ± 12.6	58.7 ± 11.8†‡
BW (kg)	74.9 ± 11.5	74.6 ± 11.7	74.2 ± 11.4	73.6 ± 11.5	72.3 ± 11.0*†

*$p < 0.01$ vs. baseline. †$p < 0.05$ vs. day 8 of placebo. ‡$p < 0.001$ vs. baseline. §$p < 0.01$ vs. day 8 of placebo. ¶$p < 0.001$ vs. corresponding day of placebo treatment. ‖$p < 0.001$ vs. day 8 of placebo. Data are presented as the mean value ± SD.

BUN = blood urea nitrogen; BW = body weight; DBP = diastolic blood pressure; HR = heart rate; mPAP = mean pulmonary artery pressure; SBP = systolic blood pressure; SCr = serum creatinine; SK = serum potassium; SNa = serum sodium; UCr = urinary creatinine; UK = urinary potassium; UNa = urinary sodium; UV = urinary volume; VP = venous pressure.

TxA_2 inhibitors in the treatment of CHF. To do so, clinical trials must be expressly designed to address this aspect.

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REFERENCES

1. Holmer SR, Riegger AJ, Notheis WF, Kromer EP, Kochsiek K. Hemodynamic changes and renal plasma flow in early heart failure: implications for renin, aldosterone, norepinephrine, atrial natriuretic peptide and prostacyclin. Basic Res Cardiol 1987;82:101–8.
2. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis and pregnancy. N Engl J Med 1988;319:1065–72.
3. Stewart DJ, Cernacek P, Costello KB, Rouleau JL. Elevated endothelin-1 in heart failure and loss of normal response to postural change. Circulation 1992;85:510–7.
4. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. Circ Res 1981;63:645–51.
5. Merrill AJ. Mechanisms of salt and water retention in heart failure. Am J Med 1994;6:357–61.
6. Ichikawa I, Pfeffer JM, Pfeffer MA, Hostetter TH, Brenner BM. Role of angiotensin II in the altered renal function of congestive heart failure. Circ Res 1984;55:669–75.
7. Cody RJ, Ljungman S, Covit AB, et al. Regulation of glomerular filtration rate in chronic congestive heart failure patients. Kidney Int 1988;34:361–7.
8. Riegger AJ. Role of prostaglandins in regulation of kidney function in heart failure. Herz 1991;16:116–23.
9. Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia. N Engl J Med 984;310:347–52.
10. Castellani S, Paladini B, Paniccia R, et al. Increased renal formation of thromboxane A_2 and prostaglandin $F_{2\alpha}$ in heart failure. Am Heart J 1997;133:94–100.
11. Cirino M, Morton H, MacDonald C, Hadden J, Ford-Hutchinson AW. Thromboxane A_2 and prostaglandin endoperoxide analogue effects on porcine renal blood flow. Am J Physiol 1990;258:F109–14.
12. Schnackenberg CG, Welch WJ, Wilcox CS. TP receptor-mediated vasoconstriction in microperfused afferent arterioles: roles of O_2 and NO. Am J Physiol 2000;279:F302–8.
13. Hably C, Menz V, Bartha J. Cardiac output distribution and intrarenal hemodynamics: role of thromboxanes. Acta Physiol Hung 1991;78:89–98.
14. Welch WJ, Wilcox CS. Potentiation of tubuloglomerular feed-back in the rat by thromboxane mimetic. J Clin Invest 1992;89:1857–65.
15. Zipser RD. Effects of selective inhibition of thromboxane synthesis on renal function in humans. Am J Physiol 1985;248:F753–6.
16. Modesti PA, Cecioni I, Colella A, Costoli A, Paniccia R, Neri Serneri GG. Binding kinetics and antiplatelet activities of picotamide, a thromboxane A_2 receptor antagonist. Br J Pharmacol 1994;112:81–6.
17. Balsano F, Violi F, the ADEP Group. Effect of picotamide on the clinical progression of peripheral vascular disease: a double-blind placebo-controlled study. Circulation 1993;87:563–9.
18. Giustina A, Perini P, Desenzani P, et al. Long-term treatment with the dual antithromboxane agent picotamide decreases microalbuminuria in normotensive type 2 diabetic patients. Diabetes 1998;47:423–30.
19. Cocozza M, Picano T, Oliviero U, Russo N, Coto V, Milani M. Effects of picotamide, an antithromboxane agent, on carotid atherosclerotic evolution: a two-year, double-blind, placebo-controlled study in diabetic patients. Stroke 1995;26:597–601.
20. Kudo K, Abe K, Chiba S, et al. Urinary excretion of TxB_2 after angiotensin converting enzyme inhibition in hypertensive patients. Prostaglandins Leukot Med 1986;21:77–86.
21. Ihara E, Hirajno K, Derkah DN, et al. The mechanism of bradykinin-induced endothelium dependent contraction and relaxation in the porcine interlobar renal artery. Br J Pharmacol 2000;129:943–52.
22. Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: the Honolulu Heart Program. Circulation 1998;98:2290–5.

23. Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983;68:302–9.
24. Currie PJ, Seward JB, Chang KL, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750–6.
25. Hussey HH, Jegers H. Practical considerations of venous pressure. N Engl J Med 1947;237:776–80.
26. Sapirstein LA, Vidt DG, Mandel MJ, et al. Volumes of distribution and clearances of intravenously injected creatine in a dog. Am J Physiol 1955;181:330–6.
27. Castellani S, Del Rosso A, Chen JL, et al. The renal excretory activity of atrial natriuretic factor is independent of renal prostaglandins in humans. Prostaglandins Leukot Essent Fatty Acids 1991;42:23–9.
28. Castellani S, Ungar A, La Cava G, et al. Renal adaptation to stress: a possible role of endothelin release and prostaglandin modulation in the human subject. J Lab Clin Med 1997;129:462–9.
29. GLM Repeated Measures. In: SPSS Advanced Models 9.0. Chicago, IL: SPSS Inc., 1999:15–32.
30. Fitzgerald GA, Pedersen AK, Patrono C. Analysis of prostacyclin and thromboxane biosynthesis in cardiovascular disease. Circulation 1983; 67:1174–7.
31. Badahaman AH, Wilson TW. A renal vasodilator effect of angiotensin II revealed by dual thromboxane inhibition. Can J Physiol Pharmacol 1994;72:632–6.
32. Zoja C, Perico N, Corna D, et al. Thromboxane synthesis inhibition increases renal prostacyclin and prevents renal disease progression in rats with remnant kidney. J Am Soc Nephrol 1990;1:799–807.